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REVIEW

Role of High-Dose Chemotherapy and Autologous Hematopoietic Cell Transplantation in Primary Systemic Amyloidosis: A Systematic Review

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Significant uncertainty exists regarding the efficacy of high-dose chemotherapy and autologous hematopoietic cell transplantation (AHCT) for the treatment of patients with primary systemic (AL) amyloidosis. We performed a systematic review and meta-analysis to evaluate the efficacy of AHCT versus conventional chemotherapy (CC) in patients with AL amyloidosis using methodology recommended by the Cochrane Collaboration. A comprehensive literature search yielded 820 studies. Twelve studies met the inclusion criteria: 1 randomized controlled trial (RCT), 2 other controlled studies, and 9 single-arm trials. The 1 RCT and 2 controlled studies compared AHCT and CC, and 9 single-arm studies assessed the efficacy of AHCT without a control. The pooled hazard ratio for overall survival (OS) in the 3 controlled studies was 1.79 (95% confidence interval [CI] = 1.11 to 2.91) favoring CC. The pooled proportion for mortality in the single-arm studies (n = 7) was 0.35 (95% CI = 0.25 to 0.46). The pooled odds ratio for complete hematologic response (CHR) from 2 controlled studies was 0.64 (95% CI = 0.25 to 1.64), indicating no difference between AHCT and CC. In the single-arm studies, the pooled proportion for CHR was 0.35 (95% CI = 0.26 to 0.44), and the pooled proportion for treatment-related mortality (TRM) was 0.12 (95% CI = 0.09 to 0.14). In the controlled studies, there was no heterogeneity for any outcome; however, in the single-arm studies, there was a significant heterogeneity for the outcomes of OS, CHR, renal response, and partial hematologic response. Our findings indicate that AHCT does not appear to be superior to CC in improving OS in patients with AL amyloidosis. But the quality of our evidence is low, indicating a need for well-designed and adequately powered RCTs to better address the role of AHCT in AL amyloidosis.

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KEY WORDS: Amyloidosis, Autologous hematopoietic cell transplantation, Systematic review, Meta analysis

INTRODUCTION

Primary systemic (AL) amyloidosis is a relatively rare systemic disorder caused by deposition of proteins derived from immunoglobulin light chain fragments in various organs. The major organs involved are kidneys, heart, and liver. Cardiac involvement often leads to significant dysfunction and poor prognosis in patients with AL amyloidosis [1]. Once the diagnosis of AL amyloidosis is established, prompt treatment is indicated to prevent irreversible organ damage [2]. Treatment for AL amyloidosis is generally similar to that for other plasma cell dyscrasias such as multiple myeloma (MM), comprising mainly various chemotherapy combinations [3-5]. In addition, high-dose melphalan (Mel) followed by autologous hematopoietic cell transplantation (AHCT) has been increasingly advocated as an effective treatment for patients with AL amyloidosis [6]. The observed benefits of AHCT in the treatment of myeloma provided a scientific rationale for evaluating a similar approach in the management of AL amyloidosis [7].

The efficacy of AHCT compared with conventional chemotherapy (CC) in treating AL amyloidosis is not known, however. Even though some studies have shown better outcomes with AHCT, whether these improved outcomes can be attributed to selection bias or are a result of AHCT per se remains unclear [8].

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To address this uncertainty, we performed a systematic review to assess the efficacy of AHCT versus CC in patients with AL amyloidosis. The primary goal of this systematic review was to synthesize and critically appraise the totality of the existing evidence on the effects of AHCT in the management of AL amyloidosis, which, to the best of our knowledge, has not been done previously.

METHODS

Literature Search

We searched the MEDLINE (PubMed) database using a broad search strategy. Our search comprised of 2 parts: methodological, aiming to locate randomized controlled trials (RCTs) [9], and specific, identifying all prospective studies related to AL amyloidosis. The studies were identified using a combination of MeSH terms related to primary systemic AL amyloidosis and therapy, such as "amyloidosis" [MeSH] or ("AL" or "primary" or "systemic" or "light chain") and "therapeutics" [MeSH] or "therapy" [subheading] also "amyloidosis" [MeSH] and "clinical trial" [MeSH] as publication type or clinical trial as topic. The search for single-arm prospective trials was limited to January 2001 through March 2008; however, the search for RCTs was performed from January 1966 to March 2008. Meeting abstracts from the American Society of Hematology (ASH), European Society of Hematology, and American Society of Clinical Oncology (ASCO) were hand-searched for the years 2001-2008.

Inclusion Criteria

An RCT was included if it evaluated the efficacy of AHCT versus CC and enrolled at least 10 patients in each arm. Nonrandomized single-arm prospective trials with or without historical controls also were included. A study was deemed eligible if it assessed at least one of the following outcomes: overall survival (OS), event-free survival (EFS), hematologic response (complete [CHR] or partial [PHR]), renal response, treatment-related morbidity, and treatment-related mortality (TRM). Retrospective studies were excluded.

Study Selection, Quality Assessment, and Data Extraction

Two reviewers (R.M. and M.B.) appraised the list of references and selected the studies in consultation with 2 other reviewers (B.D. and A.K.). Disagreements were resolved by consensus. Three reviewers (R.M., M.B., and M.K.D.) independently extracted the data from selected articles. Data were extracted on selected clinical outcomes (benefits and harms), as well as on the methodological quality of the trials.

Data Analysis and Statistical Methods

Trials with active control (RCTs and non-RCTs)

Time-to-event data and dichotomous data were pooled and reported using a random-effects model. When time-to-event data were not available for direct extraction, the hazard ratio (HR) was assessed indirectly according to the method described by Parmar et al. [10].

Single-arm trials (studies without control)

For the purpose of meta-analysis, the proportions were transformed into a quantity according to the Freeman-Tukey variant of the arcsine square root-transformed proportion [11]. The pooled proportion was calculated as a back-transform of the weighted mean of the transformed proportions, using the random-effects model.

A formal statistical test for heterogeneity was performed using the I^2 test [12]. Heterogeneity and the robustness of the findings also were explored through additional sensitivity analyses. The possibility of publication bias was investigated using the funnel plot method of Begg and Mazumdar [13] and Egger et al [14]. This method has its limitations, but nonetheless is widely used to assess publication bias [15].

The meta-analysis was done using Stata, release 9 (StataCorp, College Station, TX). The work was performed according to the guidelines published in the Quality of Reporting of Meta-Analyses statement [16].

RESULTS

Identification of Studies

The process of identifying and selecting studies for the systematic review is summarized in Figure 1. The initial search yielded 820 references. From these, 46 were selected for further full text analysis, of which 12 trials met the final inclusion criteria and were included in the final analysis (Figure 1). These 12 studies included 1 RCT [17], 2 two-arm non-RCTs (n = 2) [18,19], and 9 single-arm trials (n = 9) [20-28]. Note that van Gameren et al. [19] reported data on 2 studies, an RCT with a historical control and a single-arm trial; therefore, we cite this same reference for 2 separate studies. All of the included studies were published as full text. Characteristics of the 12 studies are summarized in Table 1.

Methodological Quality of Studies

We conducted a critical appraisal of the methodological quality of all studies according to the GRADE criteria [29].

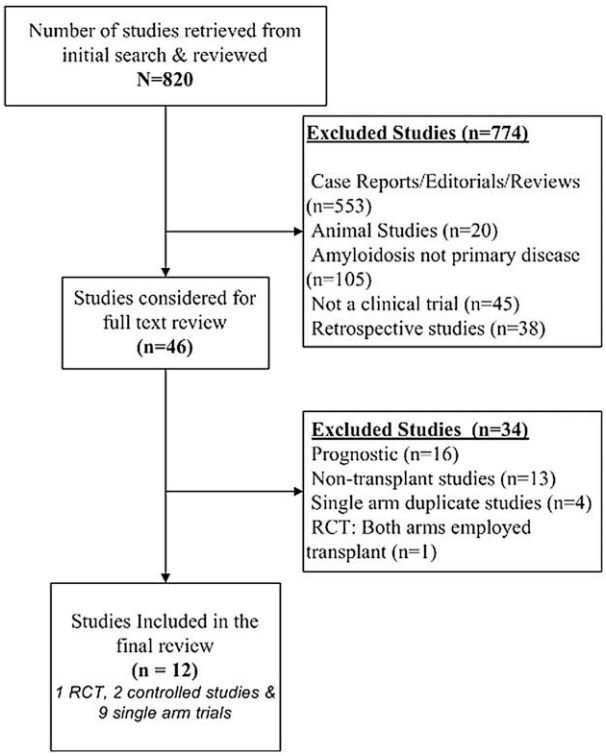

Figure 1. Flow diagram showing the process of identifying and selecting relevant studies

RCT

The method of randomization was not reported, and allocation concealment was inadequate in the RCT reported by Jaccard et al. [17]; however, the RCT did report a priori sample size calculations and adequately described withdrawals and dropouts, and the data were analyzed according to the intention-to-treat principle [17].

Non-RCTs

Altogether, 11 studies were non-RCTs. Of the 2 studies with a control arm, 1 had an active comparator [18] and the other used a historical control [19]. The remaining 9 studies were single-arm trials. All of these trials but one [23] described withdrawals and dropouts; however, only 3 of the trials (33%) [21,22,27] reported a priori sample size calculations. None of the nonrandomized studies reported a priori sample size calculations.

Study characteristics, including the eligibility criteria of the patients enrolled in the studies, are summarized in Table 1. Overall, the methodological quality of the studies was poor.

Publication Bias

Because there was only 1 RCT [17], we did not assess publication bias for RCT. The assessment for publication bias in the single-arm trials using the Begg and Egger funnel plot for the outcomes of OS, CHR, and TRM showed a symmetric distribution, indicating no publication bias (P = .85 for OS, .98 for CHR, and .10 for TRM).

Outcomes

OS

Trials with Active Control (RCTs and Non-RCTs). The pooled results for OS did not favor AHCT over CC. The pooled HR for OS in the 1 RCT and 2 non-RCTs was 1.79 (95% CI = 1.11 to 2.91; P = .018), indicating a statistically significant difference favoring CC (Figure 2). Similarly, the HR for the outcome of OS in the RCT was 1.78 (95% CI = 1.03 to 3.08; P = .04) favoring CC [18]; however, the pooled results from the 2 non-RCTs [19,20] demonstrated a statistically nonsignificant difference between AHCT and CC (HR = 1.76; 95% CI = 0.53 to 5.84; P = .35). There was a statistically nonsignificant heterogeneity among the 3 studies (I^2 = 0.00; P = .51) for the outcome of OS.

Single-Arm Trials (Studies without Control). Data on OS were extractable from 78% (7/9) of the single-arm trials. In the single-arm trials, the pooled proportion of mortality was 0.35 (95% CI = 0.25 to 0.46) (Figure 3); however, there was a statistically significant heterogeneity for the outcome of OS (I^2 = 71.5%; P = .002).

CHR

Trials with Active Control (RCTs and Non-RCTs). Data on CHR were extractable from the RCT and 1 non-RCT [17,18]. The OR for CHR was 0.64 (95% CI = 0.25 to 1.64; P = .35), indicating a statistically nonsignificant difference between AHCT and CC (Figure 4). In addition, there was no statistically significant heterogeneity in these trials for the outcome of CHR (I^2 = 0.00; P = .85).

Single-Arm Trials (Studies without Control). Data on CHR were extractable from 89% of the studies (8/9). The pooled proportion of CHR was 0.35 (95% CI = 0.26 to 0.44) (Figure 5). There was a significant heterogeneity among studies for the outcome of CHR, however (I^2 = 74.3%; P = .00).

PHR

Trials with Active Control (RCTs and Non-RCTs). The RCT [17] reported data only on PHR and demonstrated no difference between AHCT and CC. The OR was 0.35 (95% CI = 0.06 to 2.10; P = .25).

Single-Arm Trials (Studies without Control). PHR was reported in 33% (3/9) of the single-arm studies [19,21,26] and ranged from 8% [21] to 78% [19]. The pooled proportion of PHR from the single-arm trials was 0.34 (95% CI = 0.17 to 0.50). There was a statistically significant heterogeneity among these, however (I^2 = 85.7%; P = .00).

Table 1. Characteristics of Included Studies

Author	Patient Characteristics	Intervention	Comparison	Primary Outcome	Number of Institutions Involved	Methodological Quality
Study design: RCT						
Jaccard et al., 2007 [17]	n = 100 (SCT, 50; M-Dex, 50) Age: 58 (40-69) years Male, n = 57; female, n = 43 ECOG status: 0-2	IV HDM + ASCT	Oral Mel + oral Dex (M-Dex)	OS: HR = 1.78 (95% CI = 1.03 to 3.08)	Multicenter international	a priori sample size calculations: Yes Randomization method: Not reported Allocation concealment: Not adequate/unclear Dropouts described: Yes Intention-to-treat analysis: Yes
Study design: Nonrandomized 2-arm RCT						
Gono et al., 2004 [18]	n = 31 Age: 59.5 (44-78) years Male, n = 17; female, n = 14 SWOG status: 0-2	VAD + Mel + ASCT	VAD	OS: HR = 0.80 (95% CI = 0.14 to 4.61)	Single institution	a priori sample size calculations: No Dropouts described: Yes Intention-to-treat analysis: No
Van Gameren et al., 2002 [19]	n = 18 Age: 53 (43-62) Male, n = 9; female, n = 9 SWOG status: 0-2	VAD + HDM + ASCT	Mel + predisnone (MP) (historical control)	OS: HR = 2.83 (95% CI = 0.82 to 9.77)	Single institution	a priori sample size calculations: No Dropouts described: Yes Intention-to-treat analysis: Yes
Study design: Single arm without control						
Gertz et al., 2004 [22]	n = 30 Age: 54 (42-71) years Male, n = 20; female, n = 8 ECOG status: 0-2	SCT+IV Mel Mel:	Not applicable	OS: Proportion = 0.39 (95% CI = 0.19 to 0.59)	Multicenter trial	a priori sample size calculations: Yes Drop-outs described: Yes Intention-to-treat analysis: No (for response)
Gertz et al., 2002 [24]	n = 66 Age: 54 (31-70) years Male, n = 37; female, n = 29	SCT + IV Mel Mel Also, 17 patients received Mel + total body irradiation (12 Gy)	Not applicable	OS: Proportion = 0.21 (95% CI = 0.11 to 0.32)	Single institution	a priori sample size calculations: No Drop-outs described: No Intention-to-treat analysis: Yes
Blum et al., 2003 [20]	n = 13 Age: 56 (35-67) years Male, n = 8; female, n = 5 ECOG status: 0-2	Chemotherapy + peripheral blood stem cell transplantation + total body irradiation + ASCT For chemotherapy, Dex alone was recommended, but other regimens were permitted including Mel/prednisone, VAD, and VMCP	Not applicable	OS: Proportion = 0.54 (95% CI = 0.23 to 0.85)	Single institution	a priori sample size calculations: No Drop-outs described: Yes Intention-to-treat analysis: Unclear

Skinner et al., 2004 [28]	n = 394 Age: 56.9 (0-80) years Male, n = 232; female, n = 162 SWOG status: < 2	IV Mel + ASCT Mel	Not applicable	OS: Proportion = 0.44 (95% CI = 0.39 to 0.50)	Single institution	a priori sample size calculations: No Drop-outs described: Yes Intention-to-treat analysis: Unclear
Perz et al., 2004 [26]	n = 28 Age: 54 (34-65), years Male, n = 19; female, n = 9 WHO status: 0-2	2-5 cycles of VAD followed by HDM + ASCT	Not applicable	OS: Proportion = 0.29 (95% CI = 0.10 to 0.47)	Single institution	a priori sample size calculations: No Drop-outs described: Yes Intention-to-treat analysis: Unclear
Perfetti et al., 2006 [25]	n = 22 Age: 51 (31-65) years Male, n = 16; female, n = 6 ECOG status: 0-2	IV HDM + ASCT Mel	Not applicable	OS: Proportion = 0.50 (95% CI = 0.27 to 0.73)	Single institution	a priori sample size calculations: No Drop-outs described: Yes Intention-to-treat analysis: Yes
Sanchorawala et al., 2007 [27]	n = 62 Age: 55.5 (32-65) years Male, n = 40; female, n = 22 SWOG status: < 2	HDM + SCT, 2 cycles	Not applicable	OS: Data not extractable. CHR: Proportion = 0.56 (95% CI = 0.43 to 0.70)	Single institution	a priori sample size calculations: Yes Drop-outs described: Yes Intention-to-treat analysis: Unclear
Cohen et al., 2007 [21]	n= 45 Age: 57 (34-73) years Male, n = 23; female, n = 22	Mel + SCT Mel followed by adjuvant therapy with Dex + Thal	Not applicable	OS: Proportion = 0.24 (95% CI = 0.11 to 0.38)	Single institution	a priori sample size calculations: Yes Drop-outs described: Yes Intention-to-treat analysis: Yes
Gertz et al., 2007 [24]	N = 282 Age: 55-59 years (median age not extractable) Data on males and females enrolled not extractable.	HDM + SCT	Not applicable	OS: Data not extractable. CHR: Proportion = 0.33 (95% CI = 0.27 to 0.39)	Single institution	a priori sample size calculations: No Drop-outs described: Yes Intention-to-treat analysis: Yes

Mel, melphalan; HDM, high-dose melphalan; Dex, dexamethasone; ASCT, autologous stem cell transplantation; VAD, vincristine + adriamycin + dexamethasone; Thal, thalidomide; VMCP, vincristine + melphalan + cyclophosphamide + prednisone; SWOG, South West Oncology group; ECOG, Eastern Cooperative Oncology Group.

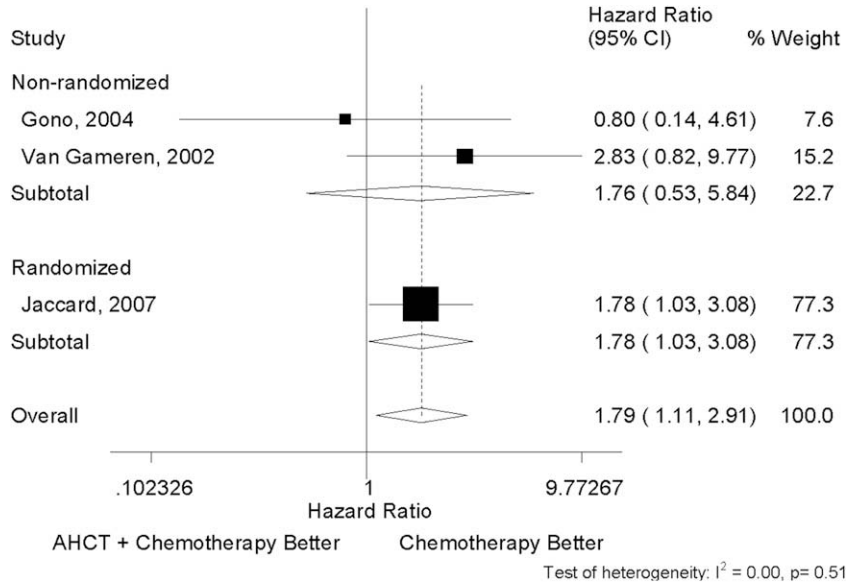

Figure 2. Forest plot of OS with CC and AHCT versus CC for AL amyloidosis. The summary effect estimates (HR) for individual RCTs are indicated by black rectangles, with the size of the rectangle proportional to the study weight; the lines represent 95% CIs. The overall summary effect estimates (HR) and 95% CIs are indicated by the diamond.

Renal response

Trials with Active Control (RCTs and Non-RCTs). Renal response was reported in the RCT [17]. The OR for renal response was 0.88 (95% CI = 0.30 to 2.53; $P = .80$), indicating no difference between AHCT versus CC. Data on renal response were not extractable from the 2 non-RCTs [18,19].

Single-Arm Trials (Studies without Control). Data on renal response were extractable from 33% (3/9) of the single-arm studies [21,26,30]; the renal response ranged from 21% [30] to 50% [26]. The pooled proportion of renal response was 0.34 (95% CI = 0.15 to 0.52). There was a statistically significant heterogeneity among the studies, however ($I^2 = 70.8\%$; $P = .03$).

TRM

Trials with Active Control (RCTs and Non-RCTs). The RCT [17] reported a TRM of 24% (9/37) with the use of AHCT, compared with 0% (0/43) with CC. The risk ratio for TRM was 22.0 (95% CI = 1.324 to 365.5; $P = .03$), indicating

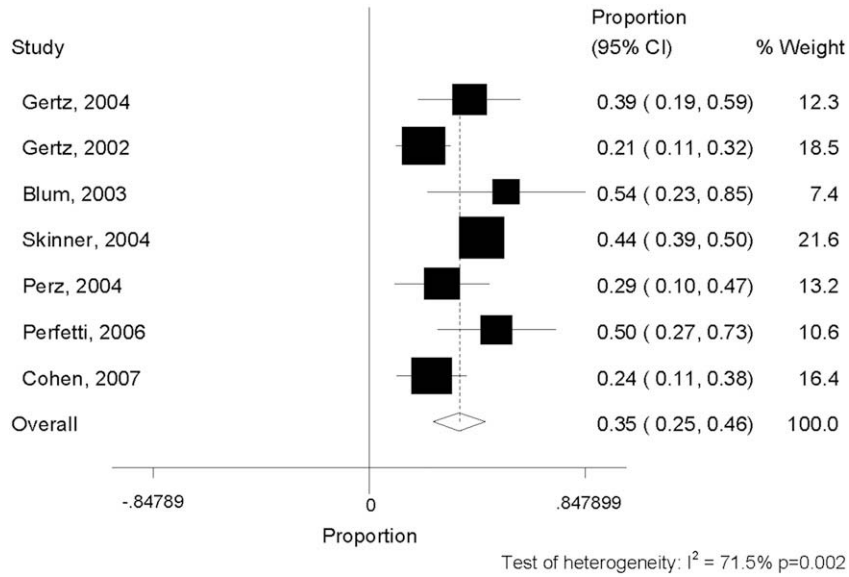

Figure 3. Forest plot for proportion of deaths in CC and AHCT for AL amyloidosis. The summary effect estimates (proportion: number of patients who died by number of patients who received the treatment) for individual studies are indicated by black rectangles, with the size of the rectangles proportional to the study weight; the lines represent 95% CIs. The overall summary effect estimate (proportion) and 95% CI are indicated by the diamond.

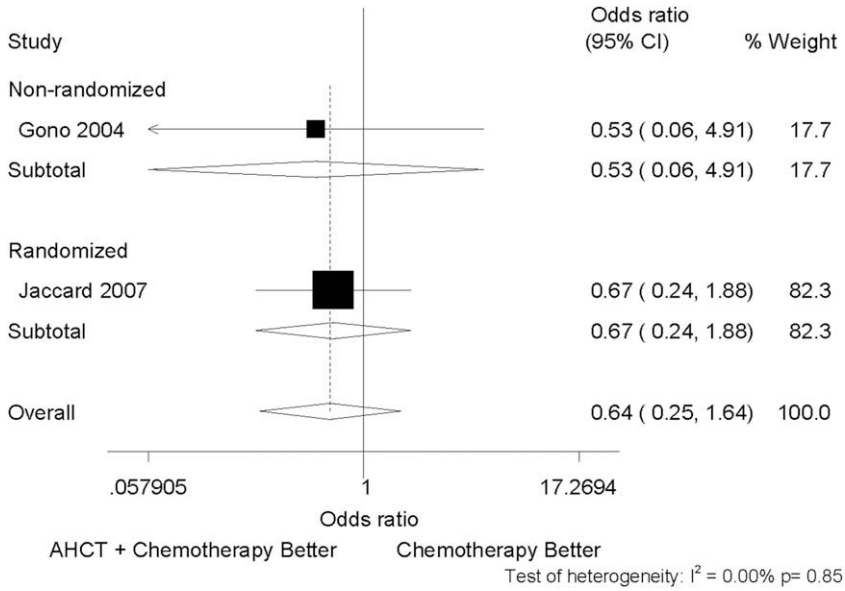

Figure 4. Forest plot of CHR with CC and AHCT versus CC for AL amyloidosis. The summary effect estimates (OR) for individual RCTs are indicated by black rectangles, with the size of the rectangles proportional to the study weight; the lines represent 95% CIs. The overall summary effect estimates (OR) and 95% CIs are indicated by the diamond.

a statistically significant risk with the use of AHCT. Data on TRM were not extractable from the other controlled studies [18,19].

Single-Arm Trials (Studies without Control). Data on TRM were extractable from 82% (9/11) of the single-arm studies. The pooled proportion of TRM with AHCT was 0.12 (95% CI = 0.09 to 0.14) (Figure 6). There was no statistically significant heterogeneity among the studies, however (I^2 = 0.00; P value = .56).

Treatment-related morbidity

Trials with Active Control (RCT and Non-RCTs). Data on treatment-related morbidity were not reported in the RCT [17]. Infections resulting from cytomegalovirus (CMV) or *Pneumocystis carinii* occurred in 21% (3/14) of the patients on the AHCT arm (compared with none in the CC arm) in the non-RCT reported by Gono et al. [18]. In the study reported by van Gameren et al. [19], 100% (12/12)

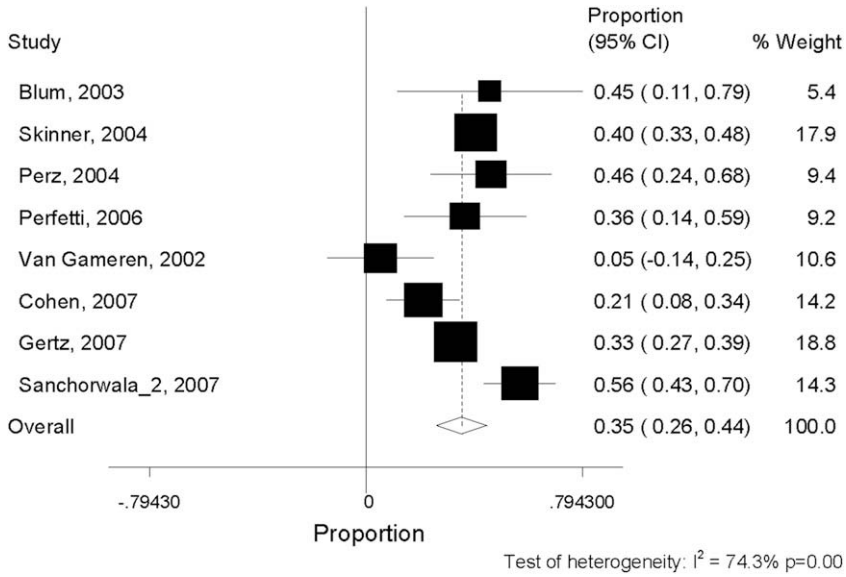

Figure 5. Forest plot for proportion of CHR in CC and AHCT for AL amyloidosis. The summary effect estimates (proportion: number of patients with CHR by number of patients receiving the treatment) for individual studies are indicated by black rectangles, with the size of the rectangles proportional to the study weight; the lines represent 95% CIs. The overall summary effect estimate (proportion) and 95% CI are indicated by the diamond.

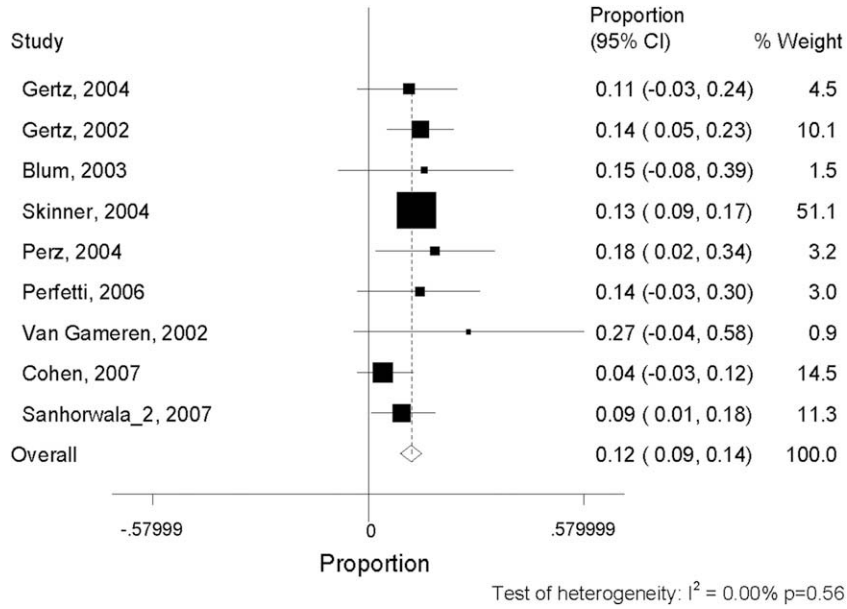

Figure 6. Forest plot for proportion of TRM in CC and AHCT for AL amyloidosis. The summary effect estimates (proportion: number of patients dying from treatment- related causes by number of patients receiving the treatment) for individual studies are indicated by black rectangles, with the size of the rectangles proportional to the study weight; the lines represent 95% CIs. The overall summary effect estimate (proportion) and 95% CI are indicated by the diamond.

of patients on the AHCT arm and 0% (0/9) of those on the control arm experienced neutropenic fever and mucositis.

Single-Arm Trials (Studies without Control). In the single-arm trials, infection was the most common treatment-related morbidity (range, 14% to 63%) followed by gastrointestinal toxicity (range, 7% to 66%). In the study reported by Perz et al. [26], 61% (24/38) of the patients experienced treatment-related toxicities of central nervous system, including seizures. Acute renal failure occurred in 21% (37/173) of the patients in the study reported by Fadia et al. [30]. In the study reported by Sanchorawala et al. [27], the tandem cycle of high-dose Mel and AHCT was associated with bacterial sepsis syndrome. This occurred more commonly after the second cycle of Mel and AHCT than after the first cycle (12% vs 4%) [27].

Sensitivity analyses

Single-Arm Trials (Studies without Control). Additional sensitivity analyses were conducted to identify the reasons for the heterogeneity among the single-arm trials for the outcomes of OS, CHR, PHR, and renal response. For CHR, estimates in 3 studies [19,21,24] were considered outliers, because the results were outside the range of the pooled estimates. Removing these outliers from the pooled analysis resulted in the disappearance of a statistically significant heterogeneity (I^2 = 17.7%; P = .30). The pooled CHR after the removal of outliers was 0.45 (95% CI = 0.37 to 0.52). The reasons for the statistically significant heterogeneity for OS, PHR, and renal response among the single-arm studies could not be identified, however.

Additional sensitivity analyses according to number of institutions involved in the study (multiple institutions vs single institution), treatment regimen (eg, Mel vs vincristine + adriamycin + dexamethasone [VAD]), renal status (patients with vs without impaired renal function), or cooperative group scoring criteria (South West Oncology Group vs Eastern Cooperative Oncology Group) used for inclusion did not change any of our findings. A sensitivity analysis also was performed to address the issues related to the occurrence of zero count in individual studies and their inclusion in the meta-analysis of single-arm trials. For the outcome of CHR, the study of van Gameren et al. [19] reported CHR in 0 of 9 patients.

We conducted 3 separate sensitivity analyses. In the first analysis, we included the data from the study of van Gameren et al. [19] in the meta-analysis according to the reported number of events (ie, 0/9 patients); the pooled estimate for CHR in single-arm trials was 0.34 (95% CI = 0.18 to 0.49). In the second analysis, we included the data from that study and used the continuity correction (0.5/9.5), resulting in a pooled CHR estimate of 0.35 (95% CI = 0.26 to 044). Finally, in the third analysis, we removed the data from that study from the CHR meta-analysis, resulting in a pooled estimate of 0.39 (95% CI = 0.30 to 0.47). The pooled results for CHR reported here involve continuity correction.

DISCUSSION

Our results demonstrate that systemic AL amyloidosis remains incurable with currently available chemotherapy combinations such as Mel and prednisone [31], which are somewhat superior to placebo [32] or colchicines [33]. Thus, evidence supports a role for chemotherapy in altering the natural history of AL amyloidosis. Prognosis remains poor, however, with median survival ranging from 12 to 18 months, even worse (4 to 6 months) with cardiac involvement. In general, only < 5% of patients with AL amyloidosis survive 10 years or beyond [31].

Some studies have reported that a combination of high-dose chemotherapy and AHCT is capable of inducing clinical remissions and prolonging survival in AL amyloidosis [34,35]; however, evidence from our systematic review and meta-analysis demonstrates no superiority of this treatment regimen in patients with AL amyloidosis. In fact, as demonstrated in our results from the 2-arm trials, CC was superior to high-dose chemotherapy and AHCT in improving OS (HR = 1.79; 95% CI = 1.11 to 2.91; $P = .01$). These estimates might be biased, however, because of high dropouts in the study reported by van Gameren et al. [19], in which 6 of 18 patients refused to enroll in the AHCT arm. But even after data from van Gameren et al. were excluded, the difference in OS between CC and AHCT was not statistically significant (HR = 1.65; 95% CI = 0.98 to 2.79; $P = .06$). Nevertheless, the quality of evidence supporting this conclusion is relatively poor, demonstrating the need for future studies to investigate the role of AHCT in AL amyloidosis.

Our findings also indicate no difference in CHR between AHCT and CC in the 2-arm trials (OR = 0.64; 95% CI = 0.25 to 1.64; $P = .35$); however, this estimate might be biased, because of high TRM in the AHCT arm [17]. Similarly, our analysis of hematologic responses among the single-arm trials revealed no superiority of AHCT over CC (Figure 5). Nevertheless, the pooled proportion of CHR obtained from the single-arm trials is noteworthy (35%), likely indicating the upper feasibility limits of efficacy in selected patients.

As discussed in the discussion of the sensitivity analyses, one limitation of our analysis is related to the occurrence of zero counts in individual studies and their inclusion in a meta-analysis of single-arm trials. Many authors have addressed this issue by conducting simulation studies [36,37] and recommend conducting sensitivity analyses using several methods and continuity correction factors [37], which we have done here. In our 3 sensitivity analyses, the pooled estimate for CHR (the only outcome with a zero occurrence) for the single-arm studies was not affected.

One criteria for high-quality reporting is that data be reported in a form that allow it to be extracted and used in a quantitative research synthesis (ie, meta-analysis). In most of the studies included in this systematic review, treatment-related morbidities were not reported as events per patient and thus could not be used in the meta-analysis. That is, treatment-related morbidities were reported using statements that did not allow us to distinguish between specific adverse events occurring in multiple patients or multiple events occurring in a single patient. Finally, as discussed earlier, the quality of evidence is low, with only one small RCT (sample size n = 100) and likely selection bias in the non-RCTs.

In summary, our findings suggest that AHCT does not appear to be superior to CC in improving survival of patients with AL amyloidosis. One important limitation of this meta-analysis is the relatively small number of eligible studies, especially RCTs. Moreover, patients with AL amyloidosis have significant comorbidities, limiting their enrollment in clinical trials because of restrictive eligibility criteria. These limitations explain the limited power of our analysis. For example, the only RCT included in our systematic review enrolled a total of 100 patients, but at least 340 patients (at $\alpha = 0.05$ and $\beta = 0.2$) would be needed to detect a 15% survival advantage. Our results underscore the urgent need for well-designed RCTs with adequate power to address the existing uncertainty related to determining the most optimal treatment approach for AL amyloidosis.

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REFERENCES

1. Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. *Blood*. 1986;68:220-224.
2. Traynor AE, Noga SJ. NCCN: multiple myeloma. *Cancer Control*. 2001;8:78-87.
3. Dhodapkar MV, Hussein MA, Rasmussen E, et al. Clinical efficacy of high-dose dexamethasone with maintenance dexamethasone/alpha interferon in patients with primary systemic amyloidosis: results of United States Intergroup Trial Southwest Oncology Group (SWOG) S9628. *Blood*. 2004;104:3520-3526.
4. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood*. 2004;103:2936-2938.
5. Sanchorawala V, Wright DG, Seldin DC, et al. Low-dose continuous oral melphalan for the treatment of primary systemic (AL) amyloidosis. *Br J Haematol*. 2002;117:886-889.
6. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood*. 2002;99:4276-4282.

7. Sanchorawala V, Wright DG, Seldin DC, et al. High-dose intravenous melphalan and autologous stem cell transplantation as initial therapy or following two cycles of oral chemotherapy for the treatment of AL amyloidosis: results of a prospective randomized trial. *Bone Marrow Transplant*. 2004;33:381-388.
8. Dispenzieri A, Lacy MQ, Kyle RA, et al. Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. *J Clin Oncol*. 2001;19:3350-3356.
9. Haynes RB, McKibbon KA, Wilczynski NL, et al. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*. 2005;330:1179.
10. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17:2815-2834.
11. Stuart A, Ord J. *Kendall's Advanced Theory of Statistics*. London: Edward Arnold; 1994.
12. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
13. Begg C, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-1101.
14. Egger M, Smith DG, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
15. Peters JL, Sutton AJ, Jones DR, et al. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. *Stat Med*. 2007;26:4544-4562.
16. Moher D, Cook D, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet*. 1999;354:1896-1900.
17. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med*. 2007;357:1083-1093.
18. Gono T, Matsuda M, Shimojima Y, et al. VAD with or without subsequent high-dose melphalan followed by autologous stem cell support in AL amyloidosis: Japanese experience and criteria for patient selection. *Amyloid*. 2004;11:245-256.
19. van Gameren II, Hazenberg BP, Jager PL, et al. AL amyloidosis treated with induction chemotherapy with VAD followed by high-dose melphalan and autologous stem cell transplantation. *Amyloid*. 2002;9:165-174.
20. Blum W, Khoury H, Lin HS, et al. Primary amyloidosis patients with significant organ dysfunction tolerate autologous transplantation after conditioning with single-dose total body irradiation alone: a feasibility study. *Biol Blood Marrow Transplant*. 2003;9:397-404.
21. Cohen AD, Zhou P, Chou J, et al. Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone +/- thalidomide for systemic light-chain amyloidosis: results of a phase II trial. *Br J Haematol*. 2007;139:224-233.
22. Gertz MA, Blood E, Vesole DH, et al. A multicenter phase 2 trial of stem cell transplantation for immunoglobulin light-chain amyloidosis (E4A97): an Eastern Cooperative Oncology Group Study. *Bone Marrow Transplant*. 2004;34:149-154.
23. Gertz MA, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for the management of primary systemic amyloidosis. *Am J Med*. 2002;113:549-555.
24. Gertz MA, Lacy MQ, Dispenzieri A, et al. Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response. *Haematologica*. 2007;92:1415-1418.
25. Perfetti V, Siena S, Palladini G, et al. Long-term results of a risk-adapted approach to melphalan conditioning in autologous peripheral blood stem cell transplantation for primary (AL) amyloidosis. *Haematologica*. 2006;91:1635-1643.
26. Perz JB, Schonland SO, Hundemer M, et al. High-dose melphalan with autologous stem cell transplantation after VAD induction chemotherapy for treatment of amyloid light chain amyloidosis: a single-centre prospective phase II study. *Br J Haematol*. 2004;127:543-551.
27. Sanchorawala V, Wright DG, Quillen K, et al. Tandem cycles of high-dose melphalan and autologous stem cell transplantation increases the response rate in AL amyloidosis. *Bone Marrow Transplant*. 2007;40:557-562.
28. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med*. 2004;140:85-93.
29. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490.
30. Fadia A, Casserly LF, Sanchorawala V, et al. Incidence and outcome of acute renal failure complicating autologous stem cell transplantation for AL amyloidosis. *Kidney Int*. 2003;63:1868-1873.
31. Gillmore JD, Hawkins PN, Pepys MB. Amyloidosis: a review of recent diagnostic and therapeutic developments. *Br J Haematol*. 1997;99:245-256.
32. Kyle RA, Greipp PR. Primary systemic amyloidosis: comparison of melphalan and prednisone versus placebo. *Blood*. 1978;52:818-827.
33. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med*. 1997;336:1202-1207.
34. Gertz MA, Lacy MQ, Gastineau DA, et al. Blood stem cell transplantation as therapy for primary systemic amyloidosis (AL). *Bone Marrow Transplant*. 2000;26:963-969.
35. Sanchorawala V, Wright DG, Seldin DC, et al. An overview of the use of high-dose melphalan with autologous stem cell transplantation for the treatment of AL amyloidosis. *Bone Marrow Transplant*. 2001;28:637-642.
36. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med*. 2007;26:53-77.
37. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351-1375.